



Understanding and Improving the Case Management of Children with Severe Malaria in DR Congo, Nigeria and Uganda:

Results of the CARAMAL study – **C**ommunity **A**ccess to **R**ectal **A**rtesunate for **M**alaria

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RBM Kigali, 28th June 2022

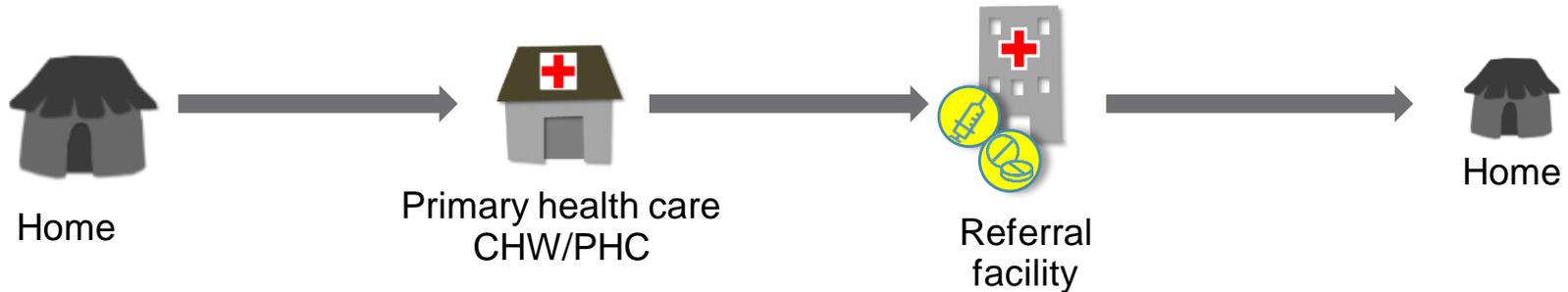
Severe malaria – a medical emergency

627,000 deaths, mainly African children, 80% in 15 countries

Parenteral **artesunate**/artemether/quinine for min. 24 hours (IM or IV)
+ full course of oral **artemisinin-based combination therapy (ACT)**



WHO 2021



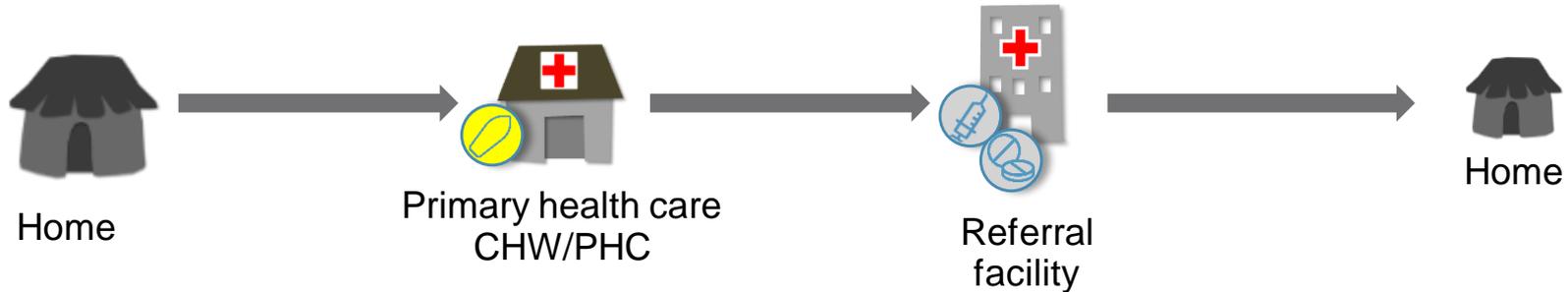
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WHO 2021



Where IM injections of artesunate are not available, treat children < 6 years with a **single rectal dose of artesunate** (10 mg/kg bodyweight), and **refer immediately** to an appropriate facility for further care.

Pre-referral rectal artesunate: prior evidence

1. In a multi-country randomised controlled trial in the mid-1990s, pre-referral RAS reduced case fatality rate in children <6 years with signs of severe malaria by 26% (short referral) to 51% (if referral took more than 6 hours) (Gomes 2009)

Context: CFR (Tanzania/Ghana) 4%, >90% referral completion, no data on post-referral care, but assumed to be good.

2. Pre-referral RAS in combination with strengthened referral and post-referral treatment reduced massively (over 90%) severe malaria CFR in one district in Zambia (Green 2019).

Context: Emergency transport system, no drug stock-outs, full health care worker training and high motivation ("ideal" conditions)

Both studies represent introduction of RAS in optimized conditions

1. What is the optimal way of rolling out RAS on a large (national) scale?
2. What is the effect of RAS implemented without major supportive interventions?

Effectiveness vs Efficacy



CARAMAL: A 3-year operational research project (2018-2020) funded by UNITAID

Goal

Contribute to **reducing malaria mortality in children** by improving the community management of cases of suspected severe malaria

Research questions

- What are **minimal health system requirements** for RAS to be effective as part of the continuum of care, from the community to a referral facility?
- What are **unintended consequences** of RAS implementation at all levels of care?
- Can the introduction of pre-referral RAS **reduce severe malaria case fatality ratio** under real-world operational circumstances?
- What are **costs** and **cost-effectiveness** of scaling up RAS?

CARAMAL population coverage

Population figures: <https://www.worldpop.org> (2018)



Project area

DR Congo



Kenge, Kingandu and Ipamu Health Zones

Nigeria



Adamawa State, Fufore, Mayo-Belwa, Song LGAs

Uganda



Apac, Kole and Oyam Districts

Total

PSS

Population

785,967

746,949

995,986

2,528,902

< 5 years

268,197

130,430

200,518

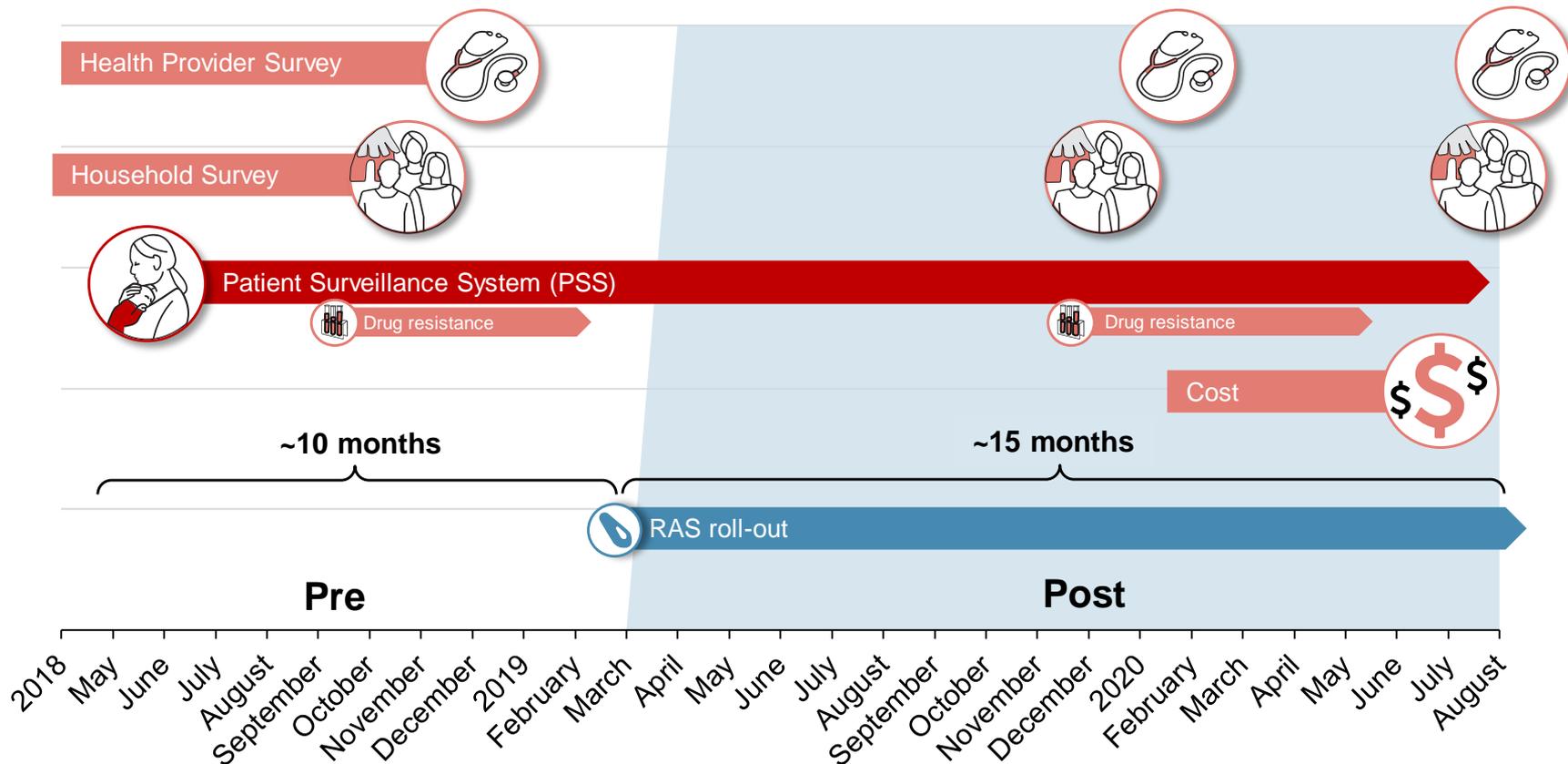
476,054

13,758

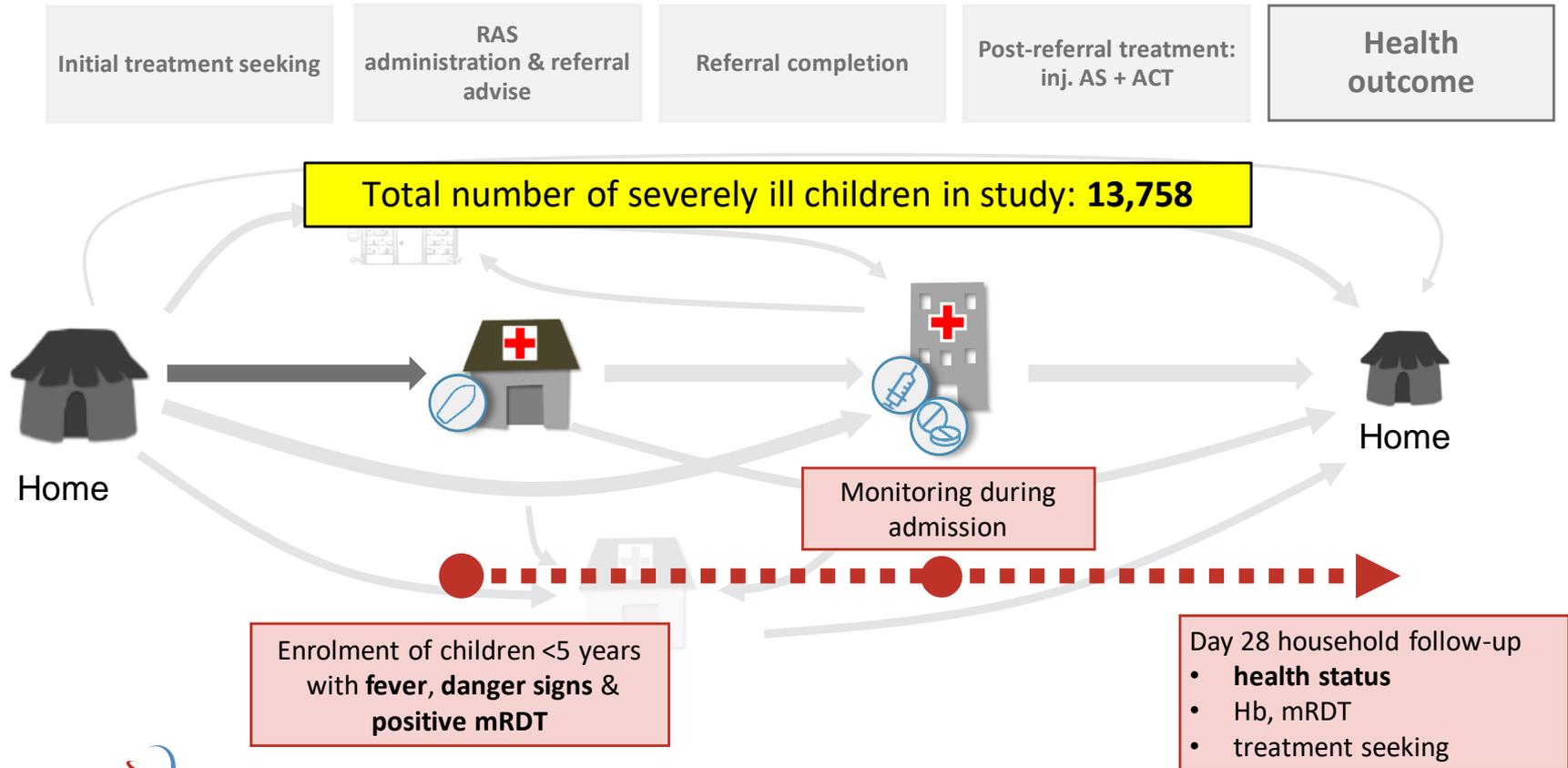
(3% of all U5 in 2 years)

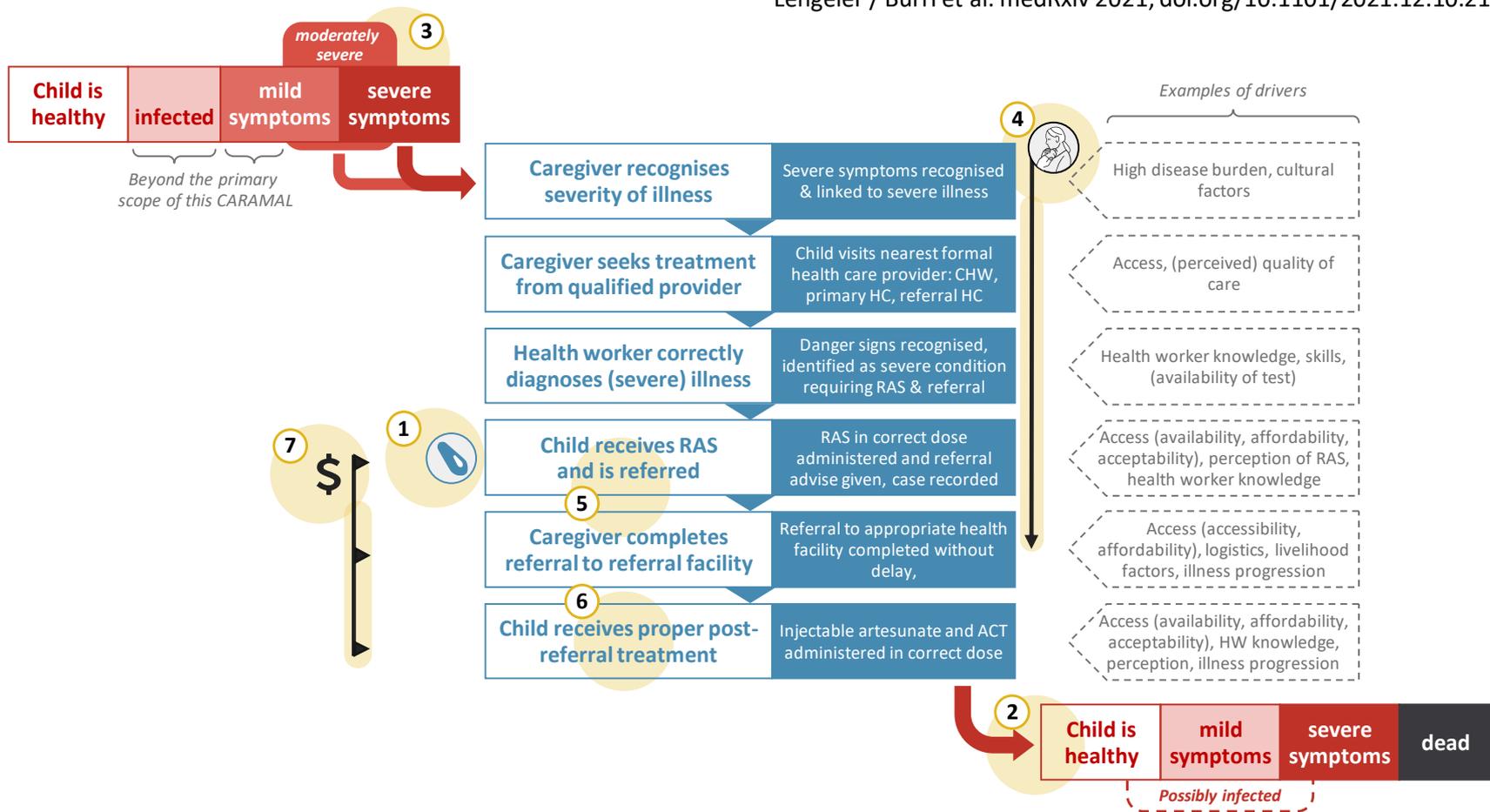
CARAMAL operational research activities

Lengeler / Burri *et al.* medRxiv 2021, doi.org/10.1101/2021.12.10.21266567



CARAMAL patient enrolment and follow-up





Key themes for analysis: 1. RAS implementation (coverage), 2. Health impact, 3. Severity of illness, 4. Treatment seeking pathways, 5. Treatment community-based providers and referrals, 6. Case management at referral facilities, 7. Costing RAS.

CARAMAL PSS study population

- ✓ Children <5 years with fever, a positive malaria test (RDT) & danger signs
- ✓ With Day 28 home visit completed
- ✓ Pre-RAS (10 months) $\approx 1/3$ Post-RAS (15 months) $\approx 2/3$

	DR Congo		Nigeria		Uganda		Overall
	Pre-RAS	Post-RAS	Pre-RAS	Post-RAS	Pre-RAS	Post-RAS	
Community health workers (CHW)	60	104	178	180	1,608	2,285	4,415
Primary health centres (PHC)	701	2,177	67	233	1	33	3,212
Referral health facilities	973	1,525	351	496	620	2,166	6,131
Total	1,734	3,806	596	909	2,229	4,484	13,758



In the field, DR Congo



Training of field workers, DR Congo



Supervision visit, Uganda



Community Health Worker Nigeria



Primary Health Care post DR Congo

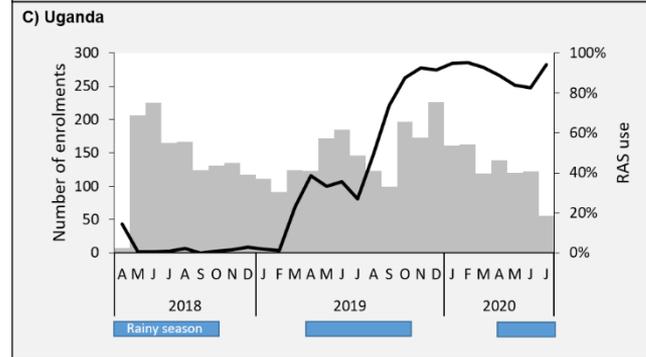
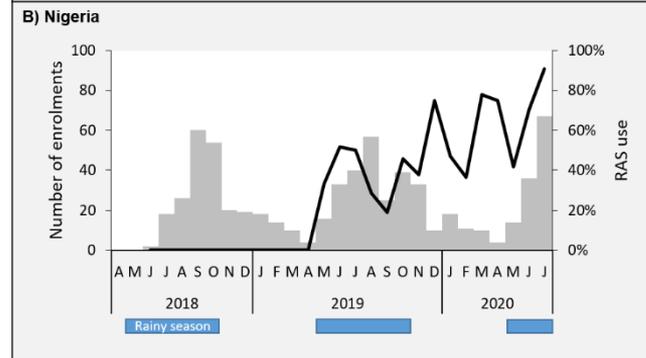
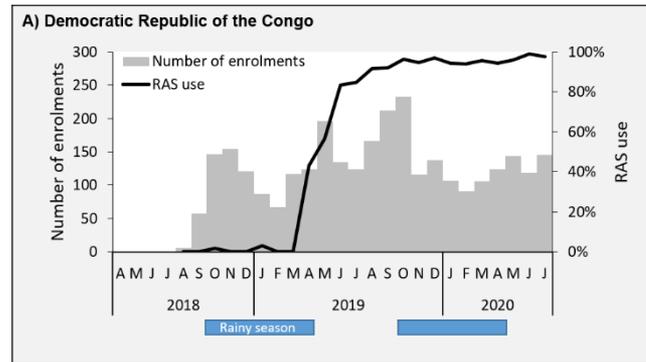


Health Center DR congo



Hospital Uganda

Study enrolment (bars) & RAS use (line)

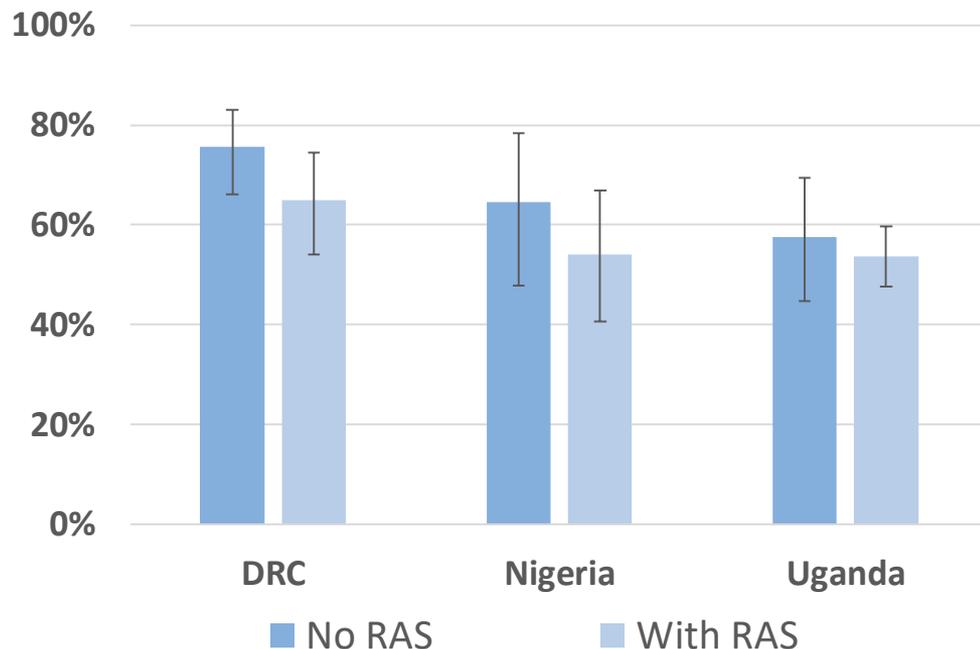


Referral rates from primary provider

Brunner et al. *BMJ Global Health* 2022;7:e008346

- ✓ In all countries, referral completion to a Referral Health Facility was slightly lower among RAS users compared to RAS non-users.
- ✓ If the use of RAS reduces referral rates, this compromises treatment and hence the survival of the children

Post-RAS



- ✓ Referral Health Facility data was analysed for 7,983 children.
- ✓ Use of injectable antimalarials was very high in all three countries (> 95%).
- ✓ A full course of an ACTs was often given in DR Congo (78.7%).
- ✓ In Uganda and Nigeria, providers were mostly given a prescription instead of the treatment, resulting in moderate levels of ACT treatment in Uganda (45.7%) and very low levels in Nigeria (1.7%).
- ✓ As a consequence, a full course of treatment at the health facility (parenteral antimalarial and an ACT) was frequent in DR Congo (76.2%), moderate in Uganda (44.7%) and low in Nigeria (1.2%).

Not completing the full course of an ACT is leading:

(1) to incomplete cure

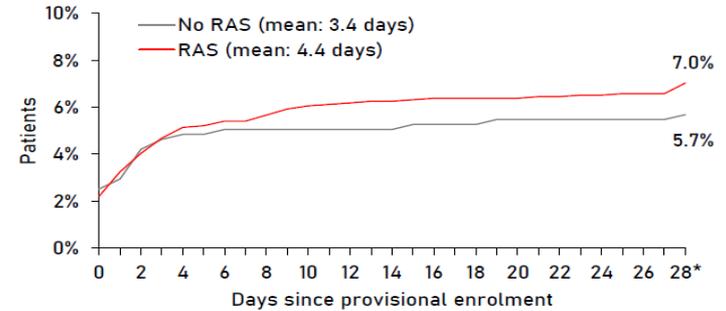
(2) to monotherapy - implying a higher risk of resistance development

Case Fatality Rates (Post-RAS)

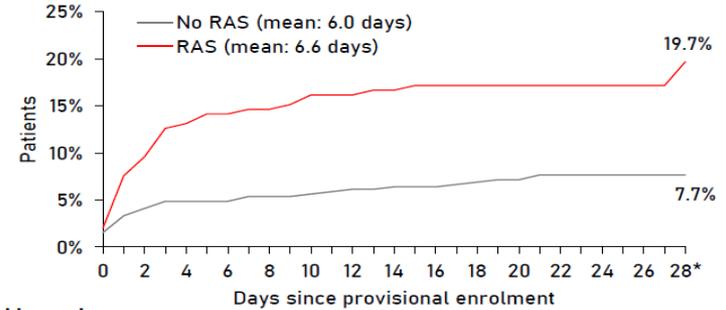
Hetzel *et al.*, medRxiv 2021.09.24.21263966

- ✓ In total 223 deaths were registered in the PSS
- ✓ The CFR was **6.7%** (135/2011) in DRC, **11.7%** (69/589) in Nigeria, and only **0.5%** (19/3686) in Uganda ($p < 0.001$)
Note difference in y-axis scales
- ✓ Usually death occurred in the days immediately after enrolment
- ✓ Mortality was higher in the RAS group, in Nigeria and marginally so in DRC

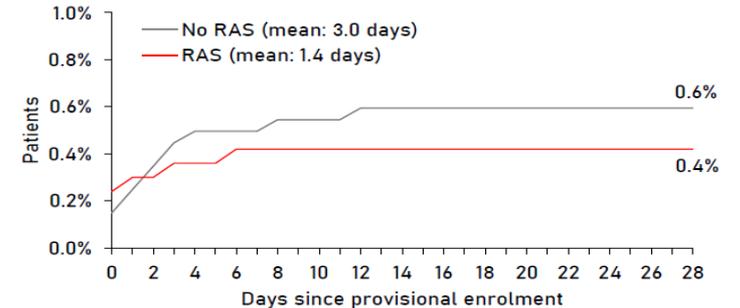
DRC



Nigeria



Uganda



Day 28 health status

Hetzel *et al.*, medRxiv 2021.09.24.21263966

- ✓ Of 6020 patients tested by mRDT (HRP2/pLDH Combo tests) at D28 follow-up, 44.0% were still positive in DRC, 50.2% in Nigeria, and 69.5% in Uganda. Most positive results likely due to remaining circulating antigen
- ✓ A substantial percentage of children were either still sick or deceased at Day 28: 19% in DRC, 17% in Nigeria, and 16% in Uganda
- ✓ This shows that patient management for severe illness cases is inadequate

- ✓ Of 2211 children included in the analysis, 96% visited a second provider after attending a CHW.
- ✓ The majority of CHWs recommended caregivers to take their child to a designated RHF (65%); however, only 59% followed this recommendation.
- ✓ Many children were brought to a private clinic (33%), even though CHWs rarely recommended this type of provider (3%).
- ✓ Children who were brought to a private clinic were more likely to receive an injection than children brought to a RHF (78% vs 51%, $p < 0.001$).
- ✓ Children who only went to non-RHF providers were less likely to receive an artemisinin-based combination therapy (ACT): OR = 0.64, 95% CI 0.51–0.79

Lessons learned: Post-referral case management

Observations

- Many children did not receive an ACT after RAS (+/- inj AS) – resulting in monotherapy treatment with low cure rate
- ACT was often provided as prescription only, expecting caregivers to purchase the medicine after discharge

Learnings and Implications

- Ensure full course of ACT is dispensed at referral facility (with at least first dose taken at facility)
 - Strengthen supply
 - Training of caregivers
 - Enforce free/low cost treatment at facilities
 - M&E for tracking treatment quality



Main conclusions

- In the CARAMAL countries, RAS - an efficacious medicine - was introduced in areas with weak health systems and impoverished communities; multiple severe system deficiencies were observed - leading to low cure rates and high case fatality rates.
- RAS is part of the continuum of care for severe malaria. Without considering the health system as a whole (including treatment seeking patterns, supplies of multiple commodities, referrals and supervision) reducing case fatality from severe malaria and other major childhood diseases is unlikely to be achieved.

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**World Health
Organization**



Spare slides



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Makerere University



Lessons learned: Treatment seeking

Observations

- Important role of chemists/drug shops (NG) and private clinics (UG)
- CHWs are often not the first source of care for cases of severe malaria

Learnings and Implications

- Private sector should be recognised as important stakeholder and equipped to provide adequate care and/or advice
- Consider RAS pre-referral treatment by private providers (e.g. accredited drug stores)
- Ensure CHWs are skilled, trusted, and recognised as first points of care *particularly where health facilities are harder to reach*
- Strengthen supply chain to ensure that commodities are available at all times (***the right drug at the right time in the right place***)



Lessons learned: Treatment at community level (CHW and PHC)

Observations

- Acceptance of RAS is good and use is high when product is available
- RAS is frequently under-dosed in children ≥ 3 years of age (one rather than two suppositories)
- Big differences between individual providers in number of patients treated with RAS – making the supply chain more difficult to manage

Learnings and Implications

- Ensure functioning supply chain and sufficient stock per provider – which needs to be balanced against relatively short shelf-life
- Functional and sustainable commodity tracking system and easy access to re-supply
- Need for regular supervision (can be effectively a way of re-supplying RAS)



Lessons learned: Referral

Observations

- Referral from CHW to PHC rather than to designated referral facility (may delay/prevent full treatment)
- Referral completion from CHW to referral facility often low (<60%)
- Referral less likely in patients treated with RAS; anecdotal evidence that children's condition improves quickly after RAS, diminishing perceived need for referral

Learnings and Implications

- Patients should be referred directly to a facility that can offer adequate post-referral treatment (in the case of severe malaria usually secondary/tertiary facilities).
- Subsidized emergency transport or social health insurance to support completion of referral
- Need “back-up plan” for children who don't complete referral to prevent deterioration and mono-therapy/incomplete cure (for example, ensure full-course ACT administration)

(Real-world scenario not considered in current recommendations)

Lessons learned: Sustained financing

Observations

- iCCM platforms are sustained by various donors (no one donor financing all the pieces); hence piecemeal approach leading to multiple stockouts (*a chain is only as strong as its weakest link*)
- “Health systems strengthening” is a donor orphan, being generally considered to be for “domestic investments” - which are usually stretched thin

Learnings and Implications

- Concerted action plan by the MOH to ensure all components of the essential continuum of care for childhood diseases are available at all times
- Progressive take over by domestic financing could ensure more continuity
- Progressive sensitization and inclusion of the private sector in the provision of proper care

